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THE clinical use of members of the polymethylene bistrimethylammonium series as agents for neuromuscular and for ganglionic block has been suggested on the basis of animal experiments (Paton and Zaimis 1948). In the following trials the decane and pentane diiodide have been used (C10 and C5 respectively). The salient features of their pharmacological actions may be summarised as follows :

(1) C10 injected in small doses into a cat or other animal causes a neuromuscular block which spares the respiratory muscles ; it is not antagonised by anticholinesterases, but a useful antidote exists, if needed, in C5 (which is virtually devoid of curarising activity). C10 has much less activity in liberating histamine or heparin (MacIntosh 1948) and has less activity in paralysing autonomic ganglia than has an equal weight of *d*-tubocurarine chloride.

(2) C5 is powerful in paralysing autonomic ganglia in cat and rabbit—as shown by block of the superior cervical ganglion, fall of blood-pressure, paralysis of the peristaltic reflex of the small intestine, and paralysis of the action of the vagus on the heart. C5 is thus similar to tetraethylammonium iodide, but it is 10–20 times more active, and its effects last two or three times as long. C5 was used for convenience in these trials, although C6 (the hexane derivative) was originally proposed. The two drugs act alike, C5 being slightly more potent as an antidote to C10, and C6 being slightly more active in paralysing autonomic ganglia.

With C10 in particular there is great variation of potency with the species of animal used for the tests. We describe here preliminary trials of C10 and C5 to ascertain the sensitivity of man to these drugs and to find whether their effects in man differ from those in other animals. This is a first step towards assessing their clinical value.

EFFECTS OF C10

Tests have been made on three volunteers (W. D. M. P., E. J. Z., and G. O.) on five occasions, on two of which C5 was also administered. C10 3 mg. was slowly injected

intravenously in 50–90 sec. In each trial the first effect noticed subjectively was on the eyes and eyelids, within 20 sec. of the beginning of the injection. Paralysis reached a maximum in about 4 min., recovery beginning in about 10 min. and being complete in 1 or 2 hours.

Paralysis began in the eyelids, ocular muscles, and facial muscles, and later affected the neck, trunk, and limbs. The degree of paralysis varied within limits among the subjects; at the peak of the paralysis two of them were incapable of moving their limbs or head at all, and had virtually complete paralysis of hand strength (figs. 1 and 2); the third was very considerably weakened, and his hand strength fell by about 60%. In all cases there was a considerable reduction in abdominal tone and in the power of contracting the abdominal muscles. The respiration, however, was not embarrassed, though the vital capacity was diminished at the peak of the paralysis by about 35%. Speech was impaired, the voice becoming weaker and lower in

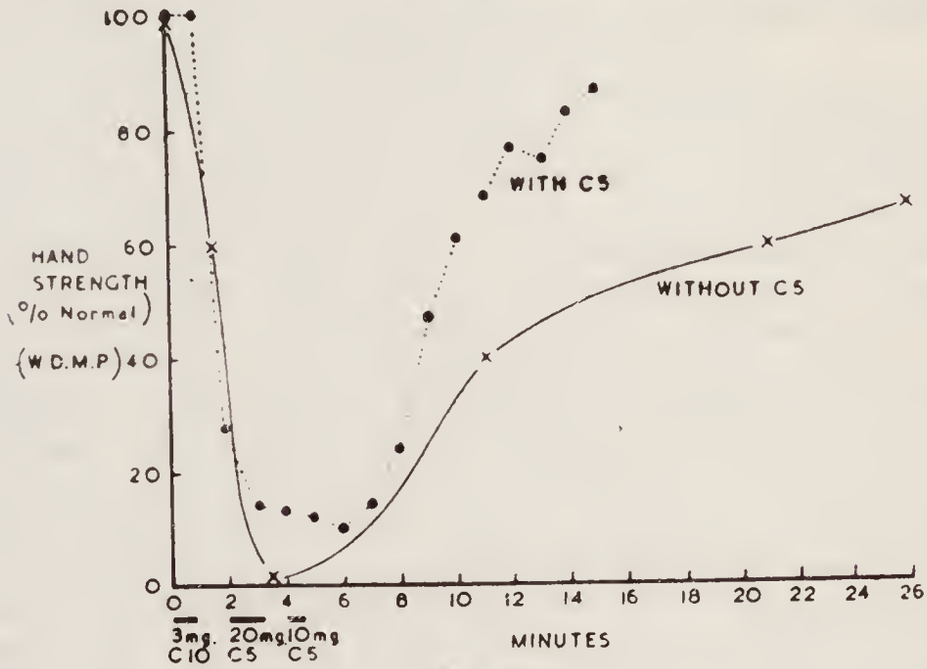

Fig. 1.

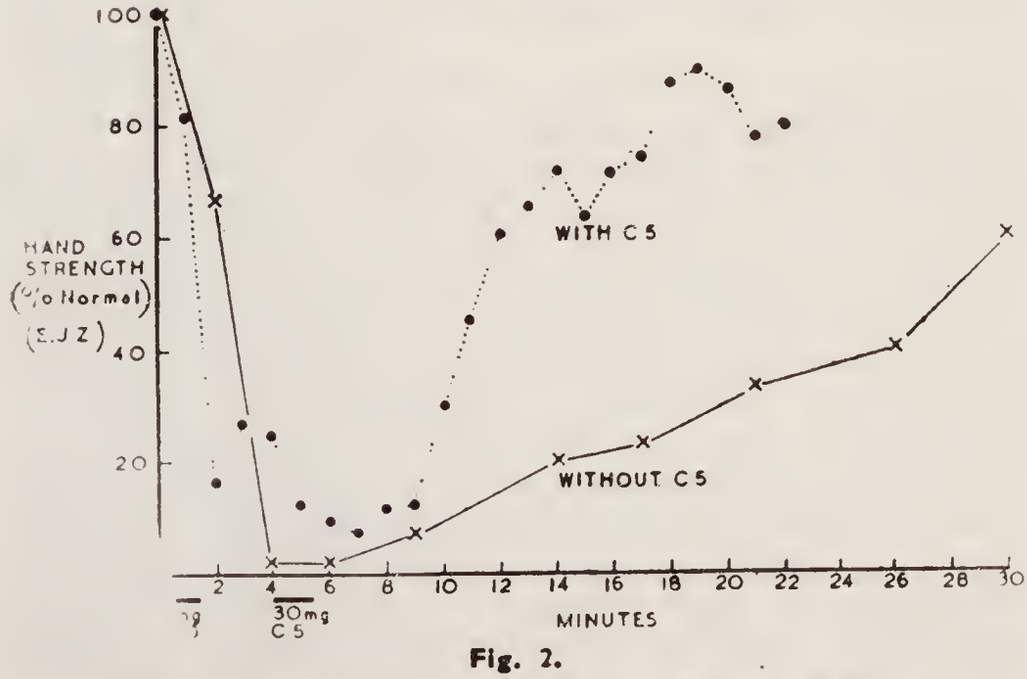

Fig. 2.

Figs. 1 and 2—Paralysis and return of hand strength.

DURATION OF PARALYSIS IN MINUTES

Power recovered	Volunteer			
	E. J. Z.		W. D. M. P.	
	C10 alone	C10 with C5	C10 alone	C10 with C5
Leg-lifting	17	8	11	9
50% hand strength	28	11	15	9
Abdominal tone ..	20	9	20	11
Ocular muscles ..	15	8	30	9
Ability to stand up..	45	26	45	20

pitch, but coughing was always possible; swallowing was weakened but never disappeared. The jaw muscles were relaxed, but there was no consequent obstruction to the respiration. The degree of paralysis was roughly comparable with that obtained in a conscious subject with 15–20 mg. of *d*-tubocurarine chloride.

Side-effects.—No important side-effects were seen. There was a rise of pulse-rate and blood-pressure, synchronous with the development of the paralysis, which began to pass off in 5 or 6 min. (probably this was of emotional origin). Electrocardiograms taken before, during, and after the paralysis were normal in every trial. Examination of the capillaries of the finger-nail bed in one subject showed a vasoconstriction starting 14 sec. after the injection, reaching a peak at 100 sec., and then returning to normal; there was no evidence of vasodilatation. Salivation was not more, but possibly less, than normal. During the beginning of the paralysis a vague feeling of slight tightness of the muscles was noted subjectively for a brief time and then passed off. C10 also appeared to have a slight narcotic action, but it was difficult to dissociate this subjectively from the effects of an almost complete motor paralysis. Sensation was normal.

The accompanying table shows the duration of paralysis in the various muscles. It must be noted, however, that it is difficult to estimate muscle strength in man quantitatively, and these times are necessarily only approximate. On the whole, the time-scale of the paralysis was similar to that of one of equivalent maximum depth due to *d*-tubocurarine chloride, except that the ocular effects do not appear to last so long.

Antagonist.—Observations on the effects of C5 alone are described below. Doses of 30 mg. given at the peak of a paralysis due to C10 substantially accelerated recovery. The first subjective sign was a sense of ease of respiration. Figs. 1 and 2 show the extent to which C5 accelerated recovery of hand strength, and the table shows the same for other muscular functions. There was no fall in blood-pressure, though there was detectable

flushing of the skin of face and hands and slight conjunctival suffusion. Electrocardiograms were normal throughout, and there were no other side-effects.

EFFECTS OF C5

C5 has been administered to three normal subjects (W. D. M. P., E. J. Z., and F. E. C.) in doses of 20–40 mg. intravenously. This did not change the blood-pressure while the persons were supine, but there was detectable flushing and warming of face and hands, together with a feeling of warmth in these places, and some conjunctival suffusion. No other effects were noticed. When the subjects stood up, however, the systolic pressure fell by 20–35 mm. and the diastolic by 5–15 mm.; in one person this fall led to a severe syncopal attack. When the subjects lay down again the blood-pressure returned to normal. Such falls in blood-pressure were obtainable by assuming the erect posture as late as 30 min. after the injection. Electrocardiograms taken during the tests were unchanged throughout.

DISCUSSION

The results show that man is very sensitive to C10, and that in this he resembles the cat rather than the monkey, rabbit, mouse, or rat. The doses of C10 required for paralysis in cat and man are almost identical We have not made direct comparisons between C10 and *d*-tubocurarine chloride as regards their respiratory actions in man, but a comparison of the descriptions of respiratory depression by *d*-tubocurarine chloride (Prescott et al. 1946; Hobson and Prescott 1947) with the results of these trials indicates that the relative sparing of respiration by C10 in the cat is found in man too. Similarly, the dose of C5 required to produce vascular effects (about 0·5 mg. per kg. of body-weight) is the same in man as in the cat, and in both species can also be seen the greater potency and longer duration of action of C5 compared with tetraethylammonium iodide. It is therefore probable that man will resemble the cat in the absence of side reactions with C10, and in his other responses to C5. The high potency of these drugs and the absence hitherto of undesirable side-effects increase the prospects of their clinical usefulness in those fields where *d*-tubocurarine chloride and tetraethylammonium iodide are of service. Full clinical trials are being undertaken under the sponsorship of the Medical Research Council, and the results will be reported later.

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